Statistical Analysis Plan Amendment 2

Study ID: 205873

Official Title of Study: A Phase 1, Randomized, Double-Blinded, Placebo-Controlled,Parallel Group Study to Evaluate the Effect of Bepirovirsen on Cardiac Conduction as Assessed by 12-lead Electrocardiogram in Healthy Volunteers

NCT number: NCT06422767

Date of Document: 16 May 2025

Information Type:	Statistical Analysis Plan (SAP)

TITLE PAGE

Protocol Title:	A Phase 1, Randomized, Double-Blinded, Placebo-Controlled, Parallel Group Study to Evaluate the Effect of Bepirovirsen on Cardiac Conduction as Assessed by 12-lead Electrocardiogram in Healthy Volunteers
Application No:	IND122685
Study Number:	205873
Compound Number:	GSK3228836
Abbreviated Title:	Study to Evaluate the Effect of Bepirovirsen on Cardiac Conduction as Assessed by 12-lead Electrocardiogram in Healthy Volunteers

Sponsor Name: GlaxoSmithKline Research & Development Limited

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VERSION HISTORY

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
SAP	19 March 2024	Version 1.0 Date: 12 Mar 2024	Not Applicable	Original version
SAP Amendment 1	17 June 2024	Protocol Amendment Version 1.0 Date: 07th June 2024	CCI [redacted]	
SAP Amendment 2	16 May 2025	Protocol Amendment Version 2.0 Date: 15th Nov 2024		

1. INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to describe the planned analysis to be included in the CSR for the Study 205873.

Descriptive study population analyses such as demography and baseline characteristics and additional detail with regards to data handling conventions and the specification of the data displays will be provided in the Output and Programming Specification (OPS) document.

1.1. Objectives, Estimands and Endpoints

Objective(s)	Endpoint(s)
Primary	
• To determine the effect of bepirovirsen exposure (from a supratherapeutic dose) on the QT interval corrected with Fridericia's formula (QTcF) in healthy participants estimated at Cmax using exposure-response modelling	• Change from baseline in QTcF under bepirovirsen exposure following a supratherapeutic single dose.
Secondary	
• To evaluate the effect of bepirovirsen exposure (from a supratherapeutic dose) on other ECG parameters	• Change from baseline in HR and QTcF, PR, and QRS intervals (ΔHR, ΔQTcF, ΔPR, and ΔQRS) using by-time point analysis (secondary analysis) • Incidence of categorical outliers for QTcF, HR, PR, and QRS • Incidence of treatment emergent changes of T wave morphology and U-wave presence
• To evaluate the PK of a single dose of bepirovirsen (CCI mg or CCI mg)	• Bepirovirsen plasma concentration and PK parameters (AUC (0-∞), AUC (0-24), Cmax, and Tmax).
Safety	
• To assess the safety and tolerability of a single dose of bepirovirsen (CCI mg or CCI mg) in healthy participants	• Occurrences of adverse events (AEs) and serious adverse events (SAEs) • Change from baseline in clinical laboratory tests and vital signs
Exploratory	
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1.1.1. Primary estimand

The primary question of interest is:

Is there a clinically significant and clinically relevant effect of bepirovirsen exposure, following a supratherapeutic dose, on cardiac conduction as measured by a change in QTcF from baseline.

The estimand is described by the following attributes:

Population	Healthy participants
Treatment	A single dose of bepirovirsen (either CCI) or matching placebo
Endpoint	Change in QTcF interval from baseline (ΔQTcF)
Summary Measure	Geometric mean and 90% confidence intervals of ΔΔQTcF (placebo-corrected change from baseline) predicted from a concentration-QT model at the Cmax following a supratherapeutic single dose (CCI mg)
Intercurrent Events	Any events leading to a non-full dose. Treatment Policy strategy will be applied to address this intercurrent event.

Rationale for Estimand: Interest lies in the overall relationship between the ΔQTcF and bepirovirsen concentrations while the participant is exposed to bepirovirsen. Therefore, even though the concentration for a dose is affected, the data are still relevant.

1.2. Study Design

Overview of Study Design and Key Features	
Design Features	This is a Phase 1, double-blind, randomized, placebo-controlled study to investigate the effect of a supratherapeutic dose of bepirovirsen on cardiac conduction, PK and safety and tolerability in healthy adult participants. A total of approximately 46 participants will be enrolled and randomized to one of the two arms in a parallel design. Participants will be screened within 28 days before Day –1 (the day before dosing). They will attend the clinical unit 2 days before dosing (Day –2) and will remain inpatient until CCI after dosing (CCI).

Overview of Study Design and Key Features	
	They will receive a single dose of bepirovirsen CCI mg (prior to protocol amendment 2) or CCI mg (protocol amendment 2 onwards) or matching placebo, in a 1:1 randomization on Day 1. Participants will return for outpatient visits CCI after dosing CCI), and for a final visit CCI days after dosing CCI). The total duration of study participation including screening for each participant will be up to CCI weeks. Blood samples will be taken to measure levels of bepirovirsen before dosing and until CCI after dosing. Time-matched ECGs recordings will be taken at all PK sampling time points. Safety and tolerability will be assessed from before dosing and until the final visit. Since the bepirovirsen CCI mg dose had not been previously administered to humans, this study was designed to include a sentinel cohort of 2 participants (1 active CCI mg bepirovirsen, 1 placebo). At least 7 days after dosing, and before further participants could be randomized, a meeting occurred between the Principal Investigator and sponsor medical monitor to review blinded sentinel cohort safety and tolerability data up to CCI . The data reviewed included AEs/SAEs, laboratory results, safety 12-lead ECGs, and vital signs. Following the sentinel cohort safety review, a second cohort of 8 participants was randomized 1:1 to receive CCI mg bepirovirsen or placebo (4 active, 4 placebo). At least 7 days after the participants were dosed, and before dosing further study participants, the GSK SRT reviewed blinded safety and tolerability data (including AE/SAEs, laboratory results, safety 12-lead ECGs, and vital signs) up to Day 4 for the 8 participants in the second cohort, as well as all available safety data from the 2 sentinel participants. Among the 10 participants dosed, 2 experienced tolerability issues related to systemic AEs. A decision was made not to dose any further participants with bepirovirsen CCI mg due to the tolerability concerns, and to reduce the bepirovirsen dose to CCI mg for all subsequent participants. The remaining 36 participants in the study will be randomised to receive either CCI mg bepirovirsen or placebo, in a CCI CCI CCI CCI
Study intervention	• CCI CCI CCI

Overview of Study Design and Key Features	
	CCI CCI CCI

Study intervention Assignment	Participants will be randomly assigned in a CCI ratio to receive study intervention. Investigators will remain blinded to each participant's assigned study intervention throughout the course of the study. To maintain this blind, an otherwise uninvolved third party will be responsible for the reconstitution and dispensation of all study intervention and will endeavor to ensure that there are no differences in time taken to dispense following randomization.
	In the event of a quality assurance audit, the auditor(s) will be allowed access to unblinded study intervention records at the site(s) to verify that randomization/dispensing has been conducted accurately.
	Investigators and site staff could infer treatment assignment due to:
	• Differences in the injection force due to the viscosity of bepirovirsen versus placebo saline.
	  ○ This is minimized using 27G thin-walled needles or 25G regular-walled needles.
	• Colour difference of bepirovirsen versus placebo saline
	  ○ Syringes will be wrapped in a coloured transparent tape to prevent unblinding of the participant and blinded site staff.

Interim Analysis	No interim analysis is planned for this study.

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2.1. Multiplicity Adjustment

No multiplicity adjustment is implemented.

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4. STATISTICAL ANALYSES

4.1. General Considerations

The Safety analysis set will be used for all study population analyses and safety analyses, unless otherwise specified. The QTc analysis set will be used for QTc analyses. The PK analysis set will be used for all PK analyses. Study population and safety tables will be displayed overall and by treatment groups.

Confidence intervals will use 90% confidence levels unless otherwise specified.

Unless otherwise specified, continuous data will be summarized using descriptive statistics: n, mean, standard deviation (std), median, minimum, and maximum. Categorical data will be summarized as the number and percentage of participants in each category.

4.1.1. Baseline Definition

For all endpoints (except as noted in baseline definitions) the baseline value will be the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. If there are multiple assessments collected at the same scheduled time, the average of these assessments will be used as the baseline.

For Safety ECGs and/or Vital Signs analyses, if the last, non-missing pre-dose values is measured in triplicate, then the subject level baseline is defined as the mean of the triplicate baseline assessments.

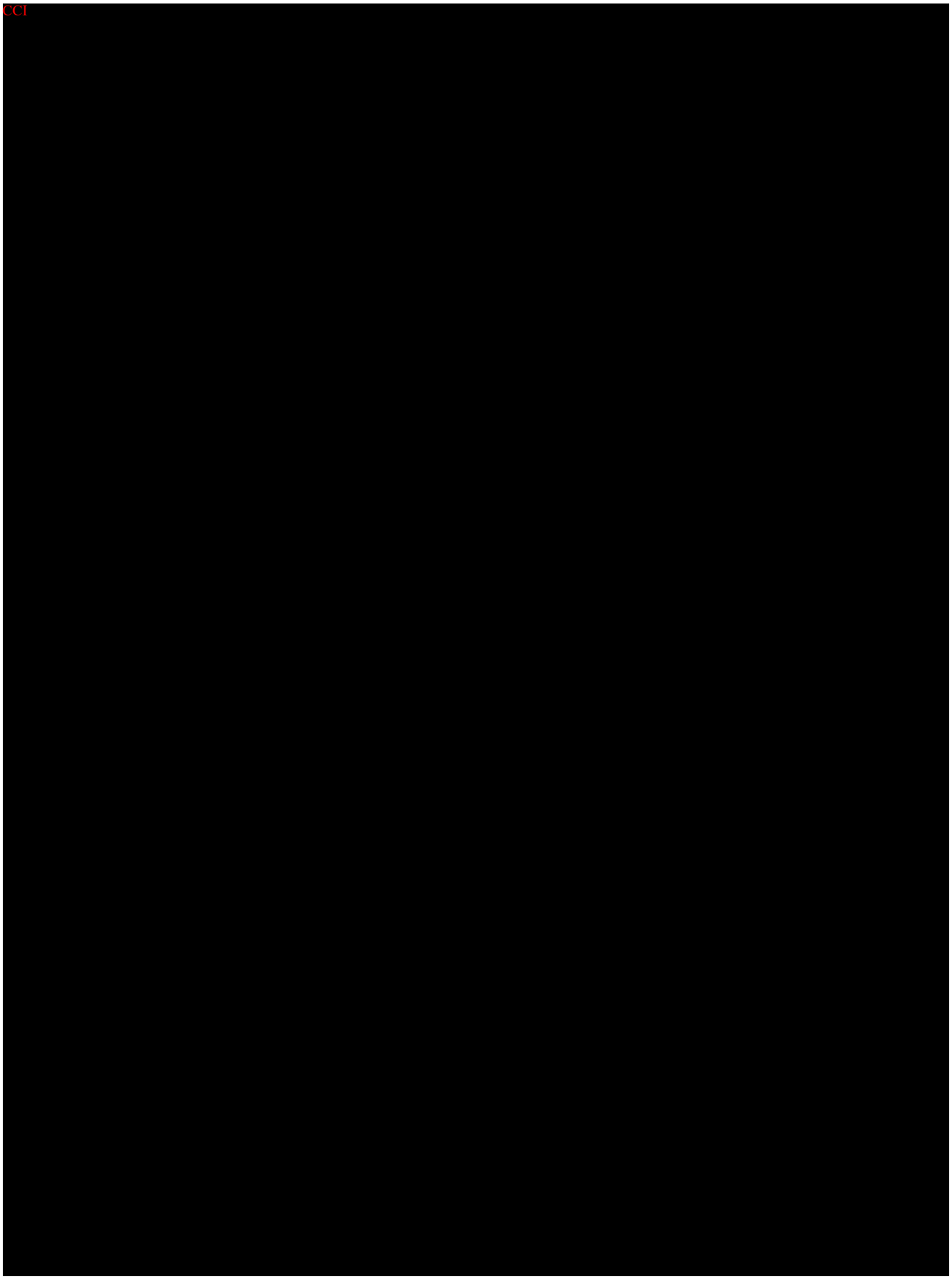
For Continuous Holter ECG collections, the pre-dose measurements at CCI [redacted] minutes taken on Day 1 will be used as the baseline value; each measurement will be taken in ten replicates, and an average value from the three timepoints will be utilized.

Blood pressure and pulse will be measured in triplicate before dosing, single measurements after dosing. Single temperature and respiratory rate measurements will be measured at all time points. When measurement is repeated at the same time point then the mean will be used.

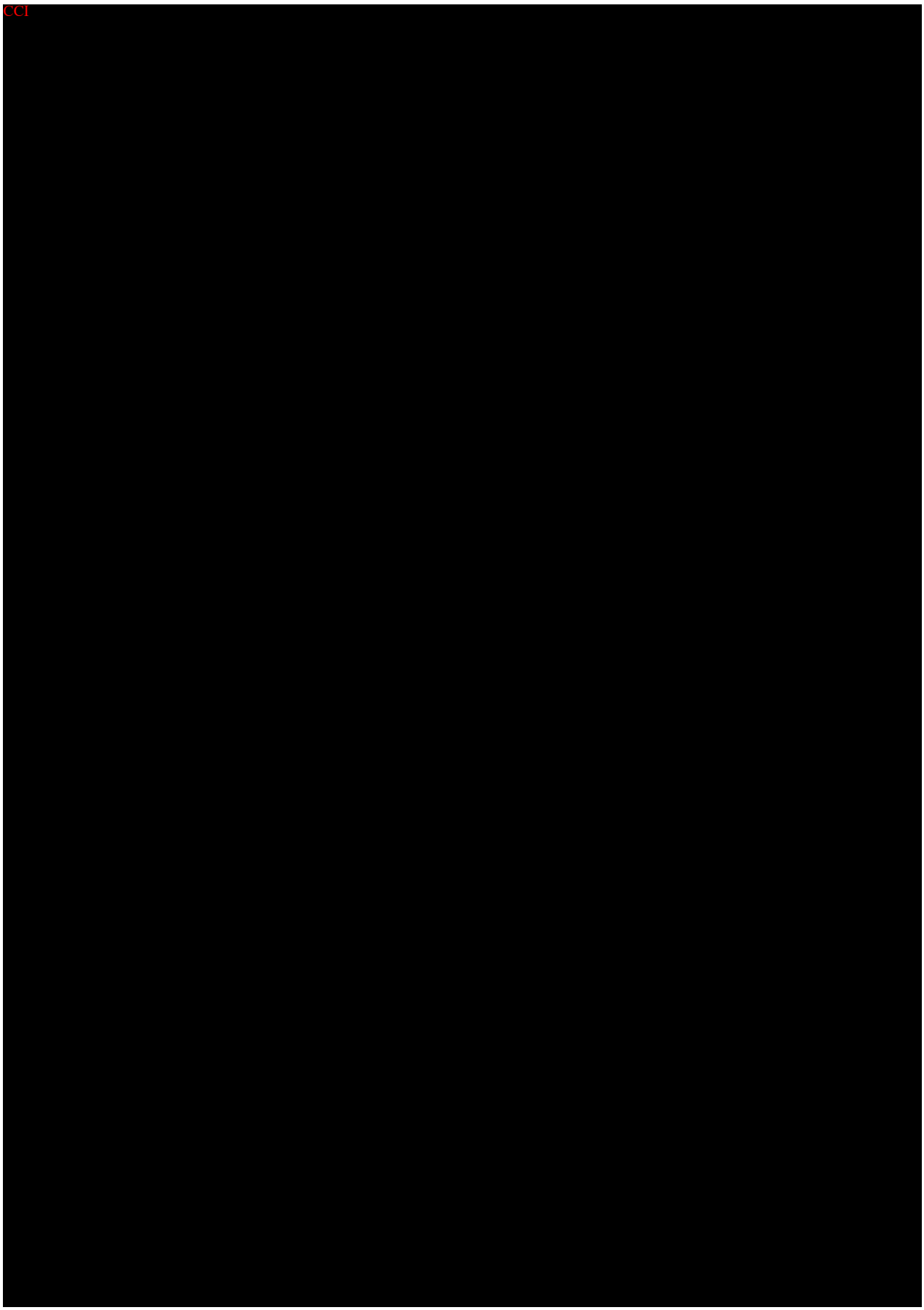
Unless otherwise stated, if baseline data is missing no derivation will be performed and baseline will be set to missing.

Baseline of serum creatinine is defined as the mean of all pre-dose values, from screening to Day 1 pre-dose assessment.

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4.2.4. Model Evaluation

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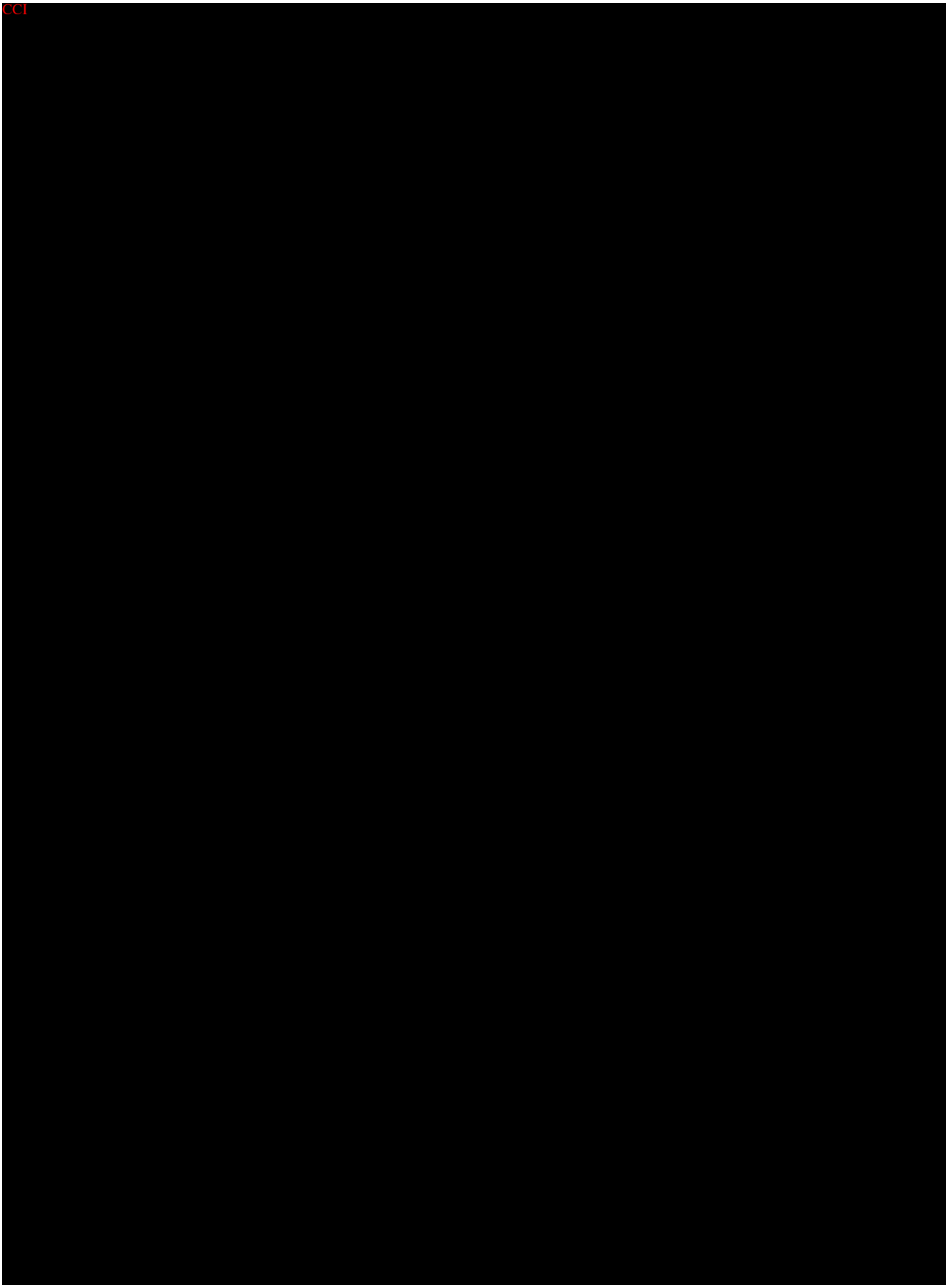
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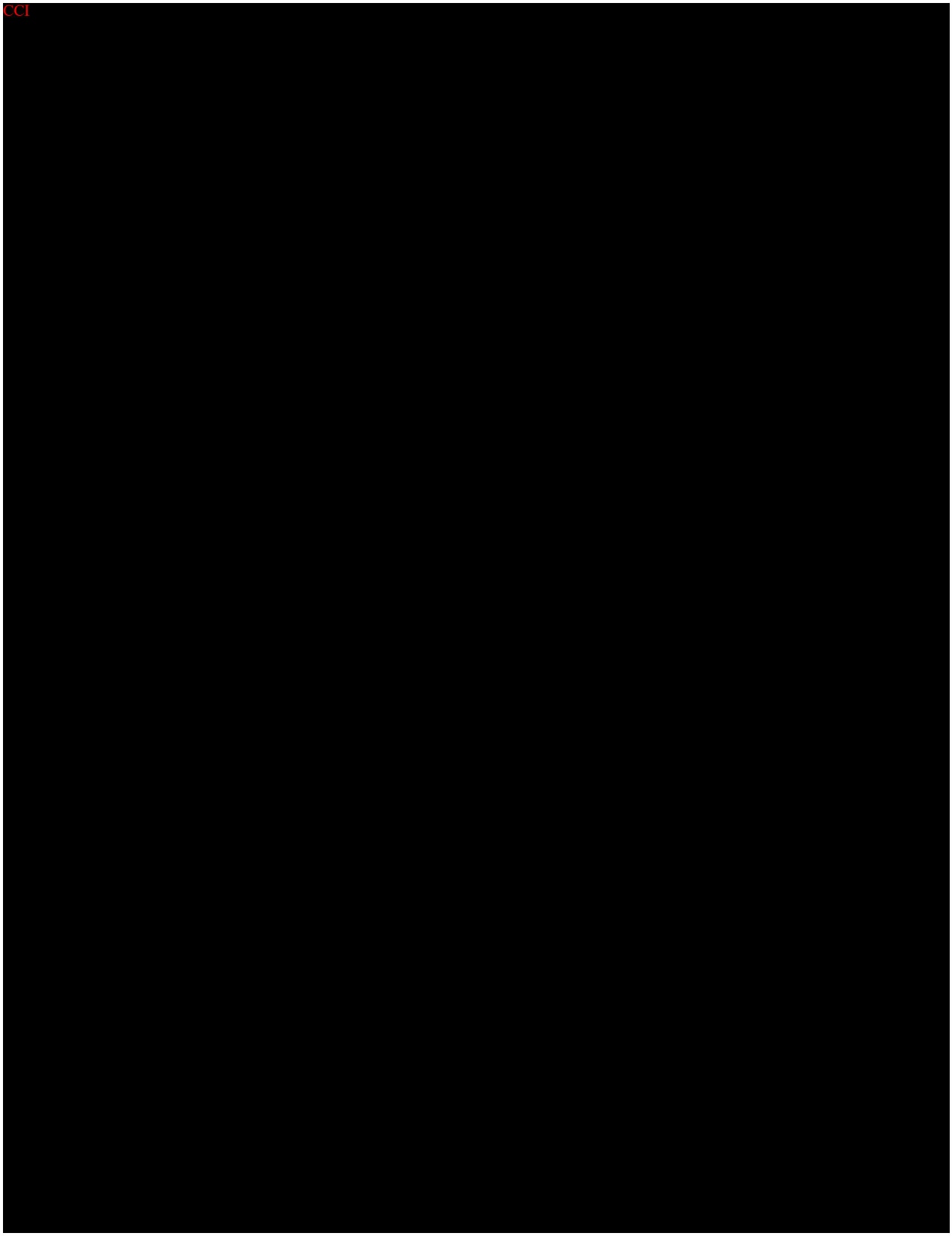
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4.3.1.2.3. Pharmacokinetic Analyses

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CCI [redacted] Statistical analysis will be performed by Biostatistics, GSK. Calculations will be based on the actual sampling times recorded during the study.

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4.4. Safety Analyses

The safety analyses will be based on the Safety Analysis Set, unless otherwise specified.

4.4.1. Adverse Events

An AE is considered treatment emergent (TEAE) if the AE onset date is on or after treatment start date. An AE is serious (SAE) if it results in death, is life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect or in other situations described in Section 10.3 Appendix 3 of the protocol.

If AE start date is completely missing and the end date is on or after the treatment start date, the AE will be assumed to be treatment emergent. All AE summaries will be based on treatment emergent events unless otherwise specified.

Adverse events will be coded using the latest version of Medical Dictionary for Regulatory Affairs (MedDRA) coding dictionary, to give a Preferred Term (PT) and a System Organ Class (SOC). These PTs and SOCs will be used when summarising the data. The severity of AEs and SAEs will be determined by the investigator according to the Division of AIDS (DAIDS) grading system Version 2.1 [National Institute of Allergy and Infectious Diseases. Division of AIDS, 2017], unless specified otherwise in the protocol.

For AEs by maximum grade summary tables, if a participant reports an AE more than once within an SOC/PT, the AE with the most severe intensity will be included in summaries. Relationship to study treatment, as indicated by the investigator, is classified as “not related” or “related”. Adverse events with a missing relationship to study treatment will be regarded as “related” to study treatment.

The following table AE summaries will be reported for each treatment group:

1. AEs overview: summary of the number and percentage of participants with any adverse event, AEs related to study treatment, any SAEs, SAEs related to study treatment, fatal SAEs and fatal SAEs related to study treatment.
2. All AEs by SOC and PT.
3. All AEs by SOC and PT and maximum grade.
4. All treatment-related AEs by SOC and PT.
5. All treatment-related AEs by SOC and PT and maximum grade.
6. SAEs by SOC and PT.
7. Treatment-related SAEs by SOC and PT.
8. AEs leading to withdrawal from the study by SOC and PT.
9. AEs leading to withdrawal from the study by overall frequency.
10 Fatal AEs by SOC and PT.
11 Serious AEs by SOC and PT (number of participants and occurrences).
12 Serious Fatal and Non-Fatal Treatment-Related AEs by overall frequency.

Number of participants with AEs will be summarized if it is not specified otherwise.

In summary tables where AEs are presented by SOC, PT, and maximum grade, SOCs will be sorted in descending order of the total incidence then alphabetically, PTs will be sorted in descending order of the total incidence then alphabetically within the SOC.

Deaths will be summarized and listed including primary cause of death.

4.4.1.1. Adverse Events of Special Interest

The following AEs of special interest (AESI) will be reported to characterise the important potential risks (safety concerns) for bepirovirsen:

- ALT increase.
- Vascular inflammation and complement activation and Immune-mediated events.
- Thrombocytopenia.
- Renal injury.
- Injection Site Reactions.

In addition, the following AEs which are identified as significant events but not as safety concerns will be reported:

- Neutropenia

An up-to-date list of standardized MedDRA Queries (SMQ)s, high level terms (HLTs) or individual PTs used to identify AESIs is periodically updated and stored in a central location. At the time of Database Lock (DBL), the latest version of the terms will be extracted and used to identify AESIs.

All AESIs and significant events will be summarized by SOC and PT, and summarized by SOC, PT, and maximum grade. Serious AESIs will be summarized by SOC and PT. All AESIs and significant events will be listed. Also, a listing of non-fatal SAEs will be produced.

Separate outputs will be created for each AESI and significant event category (ALT increase, vascular inflammation and complement activation, thrombocytopenia, renal injury, immune-mediated events, neutropenia, and injection site reactions) to explore the data in more detail if data permits.

Event Characteristics: The characteristics of all event occurrences during the post-baseline period will be summarized, which looks at event characteristics (serious, resulting in hospitalisation, drug-related, leading to withdrawal, maximum intensity, or maximum grade, fatal), number of events per participant, outcome, maximum grade or intensity and action taken. Event characteristics will be described by the proportion based on all subjects and the proportion based on subjects with the event for each of these items.

4.4.2. Additional Safety Assessments (if applicable)

4.4.2.1. Laboratory Data

Only central lab data will be used for summary analyses and figures; local lab data will be included in listings, as appropriate. The clinical laboratory tests are listed in Table 11 of protocol Section 10.2.

4.4.2.2. Laboratory Reporting

The haematology, clinical chemistry, urinalysis, and additional parameters to be tested are listed in the Appendix 2 of the Protocol.

Summary statistics for changes and percent changes from baseline for each numeric parameter at each time point will be presented, separately for all clinical chemistry (along with liver function parameters) parameters, all haematology parameters, and all urinalysis parameters. Summary statistics for actual values and changes from baseline for selected immunology parameters at each visit will be presented as indicated in the OPS.

For coagulation parameters INR, PT and aPTT, summary statistics for actual values at each visit will be presented.

Also, summaries of worst-case grade increase from baseline grade will be provided for all the lab tests that are gradable by DAIDS grading system Version 2.1 [National Institute of Allergy and Infectious Diseases. Division of AIDS, July 2017]. These summaries will display the number and percentage of participants with a maximum post-baseline grade increasing from their baseline grade. For laboratory tests that are graded for both low and high values, summaries will be done separately and labelled by direction.

For lab tests that are not gradable by DAIDS Version 2.1, summaries of worst-case changes from baseline with respect to normal range will be generated. Decreases to low, changes to normal or no changes from baseline, and increases to high will be summarized for the worst-case post-baseline. If a subject has a decrease to low and an increase to high during the same time interval, then the subject is counted in both the "Decrease to Low" categories and the "Increase to High" categories. Also, laboratory values outside of normal range will be listed.

Shift tables showing baseline toxicity versus maximum post-baseline toxicity for each grade (Grade1, Grade 2, etc.) for laboratory, chemistry, immunology, and haematology parameters will be provided.

The worst-case urinalysis results post-baseline relative to baseline will be summarized.

Increase to Grade 3 or higher lab abnormalities for platelets, ALT, AST, INR, WBC, total bilirubin, serum creatinine, eGFR, ACR will be summarized.

Scatter plots of maximum ALT vs baseline ALT as well as maximum total bilirubin vs maximum ALT will be presented. Also, plots showing mean actual and change from baseline values of the parameters over time will be presented. Listings of urinalysis data as well as lab data for subjects with values outside the normal range will also be created.

4.4.2.3. Monitoring Event Reporting

Liver monitoring and stopping event reporting will be summarized and listed. The Liver monitoring and stopping criteria are described in the protocol Section 7.1.1.

Data for potential drug induced vascular injury and complement monitoring will be captured in the eCRF; they will be summarized. The drug induced vascular injury and complement monitoring criteria are described in the protocol Section 7.1.2.

Haematological monitoring will be summarized and listed based on laboratory parameters (platelet count and anti-platelet antibodies). The haematological monitoring criteria are described in the protocol Section 7.1.3.

Data for potential Drug induced kidney injury (renal) monitoring events will be captured in the CRF; they will be summarized. The kidney injury monitoring criteria are described in the protocol Section 7.1.4.

4.4.2.4. Vital Signs

Summary statistics for absolute values and change from baseline (by each time point and treatment group) in temperature, pulse rate, respiratory rate, systolic blood pressure (SBP), diastolic blood pressure (DBP) will be provided.

Also, by-treatment summaries of grade increase in temperature, SBP and DBP will be provided separately. These summaries will display the number and percentage of

participants with any grade increase, increase to Grade 2, increase to Grade 3 and increase to Grade 4 (for temperature only), for worst case post-baseline only. The summaries will be produced for worst case post baseline only. The DAIDS grading system Version 2.1 [National Institute of Allergy and Infectious Diseases. Division of AIDS, 2017], will be used for grading:

The grade definition for temperature is: Grade 1 (38.0□C – <38.6□C), Grade 2 (38.6□C – <39.3□C), Grade 3 (39.3□C – <40.0□C), Grade 4 (≥40.0□C). The grade definition for SBP is Grade 1 (140-159), Grade 2 (160-179), Grade 3 (≥180). The grade definition for DBP is Grade 1 (90-99), Grade 2 (100-109), Grade 3 (≥110). DAIDs does not include a Grade 0, please refer to the OPS for instruction on how to present values that don't meet the criteria for Grade 1+. Participants with missing baseline values are assumed to have a normal baseline value.

4.4.2.5. Safety ECGs

When data is collected as triplicate, the average of triplicate ECG measures for each patient will be used.

Safety ECG data (absolute values and change from Baseline) will be summarised by each timepoints and treatment groups only for the end of study analysis.

4.4.2.6. Continuous Holter Monitoring

ECGs to be used in the analyses will be extracted at pre-determined time points as defined in the Schedule of Assessments (Section 1.3 of the protocol) and will be read centrally by the vendor by readers blinded to the subject and treatment allocation.

Ten 14-second digital 12-lead ECG strips will be extracted from the continuous Holter recordings using a computer-assisted process utilized by the vendor. This method enables extraction of ECGs with the lowest HR variability and noise within the specified extraction time window. The ECG replicates will be extracted over the last 5 minutes of the 15-minute supine rest period (Section 8.3.5 of the protocol) preceding the extraction time points.

QT analysis will be performed for all analysable (non-artifact) beats in the 10 ECG replicates. Statistical quality control procedures will be used to identify "high" and "low" confidence beats, based on biologically plausible thresholds, and beat to beat variability. Computer-assisted measurement of primary ECG parameters (QT, QTcF, RR) will be performed for all recorded beats that are deemed "high confidence". All low confidence beats will be reviewed manually and adjudicated. The final QC assessment is performed by a cardiologist. Beats found acceptable by manual review will be included in the analysis. The median QT, QTcF, and RR value from each extracted replicate will be calculated. The mean of all available medians from a nominal timepoint will then be used as the participant's reported value at that timepoint.

4.5. Interim Analyses

No Planned interim analysis will be conducted.

4.6. Changes to Protocol Defined Analyses

There were no changes or deviations to the originally planned statistical analysis specified in the protocol amendment 2. (Dated: [15 November 2024]).

5. SAMPLE SIZE DETERMINATION

A sample size of approximately 46 participants is chosen to obtain 42 evaluable participants to complete the study. A size of 42 evaluable participants with CCI randomization provides at least CCI to exclude that active drug caused more than a CCI effect at clinically relevant plasma levels, as shown by the upper bound of the CCI at the observed geometric mean Cmax of active drug in the study.

This power is approximated using a CCI
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CCI With a dropout rate of 10%, approximately 46 participants are planned to be enrolled to ensure the evaluable number of participants is greater than or equal to 42.

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Table 3 Sample Size Determination - Power

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6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 Study Population Analyses

Unless otherwise specified, the study population analyses will be based on the Full Analysis Set. A summary of the number of participants in each of the participant level analysis set will be provided.

Study population analyses including analyses of participant disposition, demographic and baseline characteristics, protocol deviations, and prior and concomitant medications and medical history. Details of the planned displays are presented in the OPS document.

6.1.1. Participant Disposition

A summary of the number and percentage of patients who were screened including screen failures will be provided. Reasons for failure will be included.

A summary of the number and percentage of participants who completed the study, as well as those who prematurely withdrew from the study will be provided. Reasons for study withdrawal will be summarized.

Summaries of disposition, adverse events leading to withdrawal and reasons for withdrawal will be presented, as defined in the Output and Programming Specification (OPS).

Listings of reasons for study withdrawal, screen failure will be provided.

6.1.2. Demographic and Baseline Characteristics

Demographic characteristics including sex, age, ethnicity, race, height, and weight will be summarized with descriptive statistics.

Baseline characteristics including but not limited to BMI, serum creatinine, eGFR, urine ACR, platelets, ANCA, complement C3, complement C4, C Reactive Protein will be summarized with descriptive statistics. Continuous characteristics will be presented using summary statistics (n, Mean, SD, Median, Min, Max) and may also be categorized and summarised using n (%).

Past medical conditions and current medical conditions as of screening will be summarized as “Summary of Past and Current Medical Conditions”.

Substance use, including smoking history, tobacco use, alcohol and drug history will be summarized.

6.1.3. Protocol Deviations

Important protocol deviations will be summarized and listed.

Protocol deviations will be tracked by the study team throughout the conduct of the study. These protocol deviations will be reviewed to identify those considered as important as follows:

- Data will be reviewed prior to freezing the database to ensure all important deviations are captured and categorised in the protocol deviations dataset.
- This dataset will be the basis for the summaries of important protocol deviations.

No per protocol analysis is planned for this study.

6.1.4. Prior and Concomitant Medications

Prior and concomitant medications will be coded using the newest versions of both the GSK Drug and the World Health Organization Drug Dictionary (WHODD). However, the summary will be based on GSK Drug dictionary only. The summary of concomitant medications will be provided by ingredient, i.e., multi-ingredient medications will be summarized for each individual ingredient rather than a combination of ingredients. The summary will be created using ingredient base names, i.e., ingredients with the same base name but different salt will appear under one base name in the summary. Anatomical Therapeutic Chemical (ATC) classifications will not appear in the summary, unless otherwise specified.

Concomitant medications will be summarized, where:

- A prior medication is defined as any medications that is started and ended prior to the date of single dose.
- Medications initiated after the single dose or initiated prior to the single dose and continued after the single dose will be counted as concomitant medications.

A medication that cannot be determined as prior or concomitant medication due to partially or completely missing start/stop date will be classified as the worst case, i.e., concomitant.

6.1.5. Study Intervention Compliance

Not Applicable.

6.2. Appendix 2 Data Derivations Rule

6.2.1. Study Period

Assessments and events will be classified according to the time of occurrence of relative dosing.

6.2.2. Study Day and Reference Dates

The safety reference date is the study intervention start date and will be used to calculate study day for safety measures.

The efficacy reference date is [the date of randomization OR the study intervention start date] and will be used to calculate study day for efficacy measures and baseline characteristics, as well as efficacy durations.

The study day is calculated as below:

- Assessment Date = Missing → Study Day = Missing
- Assessment Date < Reference Date → Study Day = Assessment Date – Ref Date
- Assessment Data ≥ Reference Date → Study Day = Assessment Date – Ref Date + 1

6.2.3. Assessment Window

Assessment windows are described in Table 3 of the protocol.

6.2.4. Multiple measurements at One Analysis Time Point

Mean of the measurements (e.g., ECG) will be calculated and used in any derivation of summary statistics but if listed, all data will be presented.

If there are two values within a time window the value closest to the target time for that window will be used. If values are the same distance from the target, then the mean will be taken.

Participants having both High and Low values for Normal Ranges at any post-baseline visit (including post-baseline unscheduled assessments) for safety parameters will be counted in both the High and Low categories of "Any visit post-baseline" row of related summary tables.

6.2.5. Handling of Partial Dates

Element	Reporting Detail
General	• Partial dates will be displayed as captured in participant listing displays. • However, where necessary, display macros may impute dates as temporary variables for sorting data in listings only. In addition, partial dates may be imputed for 'slotting' data to study phases or for specific analysis purposes as outlined below. • Imputed partial dates will not be used to derive study day, time to onset or duration (e.g., time to onset or duration of adverse events), or elapsed time variables (e.g., time since diagnosis). In addition, imputed dates are not used for deriving the last contact date in overall survival analysis dataset.
Adverse Events	• Partial dates for AE recorded in the CRF will be imputed using the following conventions:

Element	Reporting Detail	
	Missing start day	If study intervention start date is missing (i.e. participant did not start study intervention), then set start date = 1st of month. Else if study intervention start date is not missing: • If month and year of start date = month and year of study intervention start date, then – If stop date contains a full date and stop date is earlier than study intervention start date, then set start date= 1st of month. – Else set start date = study intervention start date. Else set start date = 1st of month.
	Missing start day and month	If study intervention start date is missing (i.e. participant did not start study intervention), then set start date = January 1. Else if study intervention start date is not missing: • If year of start date = year of study intervention start date, then – If stop date contains a full date and stop date is earlier than study intervention start date, then set start date = January 1. – Else set start date = study intervention start date. Else set start date = January 1.
	Missing end day	A '28/29/30/31' will be used for the day (dependent on the month and year).
	Missing end day and month	No Imputation

Element	Reporting Detail	
	Completely missing start/end date	No imputation
Concomitant Medications/Medical History	• Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention:	
	Missing start day	If study intervention start date is missing (i.e. participant did not start study intervention), then set start date = 1st of month. Else if study intervention start date is not missing: • If month and year of start date = month and year of study intervention start date, then – If stop date contains a full date and stop date is earlier than study intervention start date, then set start date= 1st of month. – Else set start date = study intervention start date. Else set start date = 1st of month.
	Missing start day and month	If study intervention start date is missing (i.e. participant did not start study intervention), then set start date = January 1. Else if study intervention start date is not missing: • If year of start date = year of study intervention start date, then – If stop date contains a full date and stop date is earlier than study intervention start date, then set start date = January 1. – Else set start date = study. intervention start date. Else set start date = January 1.
	Missing end day	A '28/29/30/31' will be used for the day (dependent on the month and year).

Element	Reporting Detail	
	Missing end day and month	A '31' will be used for the day and 'Dec' will be used for the month.
	Completely missing start/end date	No imputation
Age	• Age will be calculated based on the Pre-Screening Visit date (or Screening if re-screening not performed).	

6.2.6. Abbreviations & Trademarks

Abbreviation	Description
AE	Adverse Event
AESI	Adverse Event of Special Interest
ATC	Anatomical Therapeutic Chemical
AUC	Area under concentration-time curve
AUC(0-inf)	Area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time
BMI	Body Mass Index
C	Complement
CI	Confidence Interval
C_{max}	Maximum Observed Concentration
CPMS	Clinical Pharmacology Modelling & Simulation
CSR	Clinical Study Report
CV	Coefficient of Variation
DBF	Database Freeze
ECG	Electrocardiogram
eCRF	Electronic Case Record Form
FTIH	First Time in Humans
GSK	GlaxoSmithKline
HLT	High Level Term
ICE	Intercurrent Event
MedDRA	Medical Dictionary for Regulatory Activities
n	Number of participants with available data
NONMEM	Non-linear Mixed-effects Modelling

Abbreviation	Description
OPS	Output and Programming Specification
PK	Pharmacokinetic
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard Deviation
SMQ	Standardized MedDRA Query
SOC	System Organ Class
WBC	While Blood Cell

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NONMEM
SAS
WinNonlin

7. REFERENCES

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